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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/455,952	12/07/1999	GEORGE MICHALOPOULOS	A32516	5777

21003 7590 09/22/2003

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NEW YORK, NY 10112

EXAMINER
NAFF, DAVID M

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/455952	Nicholgeorgis et al
Examiner	**Group Art Unit**
Raff	1657

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence addr·ss—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DA OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 7/7/03.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 8-11, 13, 15-19 + 21-29 is/are pending in the application.

Of the above claim(s) 8-11, 13 + 15-19 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 21-29 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Applicati n Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Revi w, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

The amendment of 12/20/02 7/7/03 canceled claims 1-7, 12, 14 and 20, and added new claims 21-29.

Claims 8-11, 13 and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7 (filed 7/19/01).

Claims examined on the merits are 21-29.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The disclosure is objected to because of the following informalities: the following changes are suggested to the abstract on page 41 to make the abstract more in compliance with requirements for an abstract.

In the heading, cancel "OF THE INVENTION";

cancel line 1, and insert --- A method is provided ---;

line 2, cancel "the" and after "function" insert --- to produce a hepatic cell culture ---;

line 3, cancel "Disclosed are methods and compositions for *ex vivo* culturing of", and before "hepatocytes" insert --- A ---;

line 4, after "cells" insert --- are co-cultured *ex vivo* ---;

line 5, cancel "a";

line 9, cancel "hepatic cell culture system" and insert --- method ---, and after the period insert --- In an embodiment, the

hepatocytes and nonparenchymal cells are derived from disaggregated liver tissue and are co-cultured in the presence of epidermal growth factor or hepatocyte growth factor and beads coated with extracellular matrix protein. ---;

line 11, cancel "novel" and insert --- the ---, and cancel "system".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In (b) of claims 21, 22, 28 and 29, "matrix wherein said matrix is a bead coated with---" is confusing as to how "matrix" defines the coated bead. It is suggested that "a matrix wherein said matrix is" be deleted.

Claim Rejections - 35 USC § 103

Claims 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitaka et al (Hepatology 1999) in view of Naughton et al (5,624,840) and Vacanti et al (5,759,830) and Matsui et al (5,298,615).

The claims are drawn to a method of generating a hepatic cell culture by co-culturing hepatocytes and nonparenchymal cells derived from disaggregated liver tissue in the presence of growth factors that support the growth of hepatocytes and a matrix which is a bead coated with a biologically active molecule that promotes cell adhesion under conditions sufficient to allow for the proliferation of the hepatocytes while retaining hepatic function of the hepatocytes. Also claimed (claim 22) is the method wherein established hepatic cell lines containing hepatocytes and nonparenchymal cells are co-cultured. Further claimed (claims 28 and 29) is a population of hepatocytes and nonparenchymal cells resulting from the methods.

Mitaka et al disclose obtaining hepatic cells and nonparenchymal cells from liver tissue and culturing the hepatic cells and nonparenchymal cells together for hepatic organoid reconstruction.

Naughton et al disclose growing stromal cells on a three-dimensional matrix such as made from nylon or polystyrene (col 8, line 1) which may be coated with collagen (col 8, line 8) to form a three-dimensional stromal matrix (col 8, lines 30-40), and then growing hepatocytes on the stromal matrix to form tissue having liver function (col 11, lines 54-57).

Vacanti et al disclose growing hepatocytes (col 6, line 28) in a three-dimensional fibrous scaffold to form tissue having liver function for implanting (col 5, line 35 to col 6, line 62, and col 12, lines 17-47). The fibers of the scaffold may be coated with collagen to enhance cell attachment (col 10, lines 44-47), and epithelial cells

may be attached to the scaffold in combination with the hepatocytes (col 12, lines 25-27).

Matsui et al disclose that it is standard procedure to culture animal cells on microcarriers such as polystyrene beads coated with collagen (col 2, lines 10-25).

It would have been obvious to carry out the culturing of hepatic cells and nonparenchymal cells together as disclosed by Mitaka et al on a three-dimensional matrix or scaffold as suggested by Naughton et al and Vacanti et al to obtain the function of the matrix or scaffold in producing tissue having liver function. It would have been further obvious to provide the matrix or scaffold in the form of polystyrene beads coated with collagen as suggested by Matsui et al disclosing the use of such beads as being a standard technique for culturing animal cells. The claims do not exclude the matrix containing stromal tissue as disclosed by Naughton et al. Moreover, it would have been obvious to grow hepatocytes directly on the matrix without first forming stromal tissue when the function of stromal tissue is not needed, and since it is clear from Vacanti et al that stromal tissue can be omitted.

Response to Arguments

Applicant's arguments filed 7//7/03 have been fully considered but they are not persuasive.

Another 131 Declaration by Michalopoulos et al has been submitted to provide a statement that the "invention was conceived and reduced to practice in the United States" which was not contained in the previous declaration of 12/20/02.

The declarations fail to overcome the rejection since the claims are not commensurate in scope with the invention carrier out as shown by the exhibits of the declaration. In the invention carried out prior to January 1999 as shown by the exhibits, hepatocytes and non-parenchymal cells from disaggregated liver tissue are co-cultured on beads coated with collagen (extracellular matrix protein) to promote cell adhesion using a medium containing HGF and EGF as growth factors. The present claims encompass using substantially different growth factors and materials that promote cell adhesion. Claims 22 and 29 further differ from the method of the exhibits in not requiring the hepatocytes and non-parenchymal cells to be obtained from disaggregated liver tissue.

Amending the claims as follows would put the claims in condition for allowance.

Claims 21 and 28,

step (a), line 2 of the step, after "hepatocytes" insert --- comprising epidermal growth factor or hepatocyte growth factor, ---;

step (b),

line 1 of the step, cancel "a matrix wherein said matrix is a", change "bead" to --- beads ---, and cancel "at least one";

line 2 of the step, cancel "biologically active molecule" and insert --- extracellular matrix protein ---.

Claim 22, cancel the claim.

Claim 23, line 1, cancel "or 22", and cancel "matrix is in the form of" and insert --- beads are --.

Claim 24, cancel the claim.

Claim 25, line 1, cancel "or 22", and cancel "matrix is coated with" and insert --- extracellular matrix protein ---.

Claims 26 and 27, line 1, cancel "or 22".

Claim 29, cancel the claim.

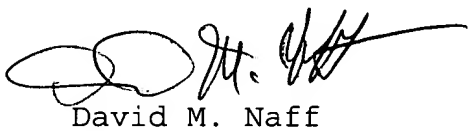
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 703-308-0520. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 703-308-4743. The fax phone number for the organization where this application is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is 703-308-0196.



David M. Naff
Primary Examiner
Art Unit 1651

DMN
9/17/03